ARMITAGE and DOLL's MULTI-STAGE MODEL for CARCINOGENSIS

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Over the past ten years there have been major advances made in cancer research in the areas of molecular biology and genetics. There has also been a considerable amount of work done in the fields of epidemiology and mathematics. It's a natural extension to transform the biological findings into mathematical relationships that help explain the cancer process.

I will be talking about one of the earliest such model that was developed by Armitage and Doll in the 1950s. It's considered a classical model that has undergone some rethinking over the last years.

ARMITAGE-DOLL MULTISTAGE MODEL

The incidence function of tumor onset at time t is given by:

$$\lambda(t) = c\,(t - w)^{k-1}$$

or

$$\log \lambda(t) = c + (k-1) \log (t-w)$$

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Incidence function = $P(T \leq t)$

c is a constant

w represents the growth of the tumor or duration

The model makes the assumption that cancer originates with a single cell that has undergone k different transformations; that the transition rates are independent; not necessarily the same for all stages; and that the order of transitions may be of importance.

Because it is recognized that for some cancers the cancer incidence increases very sharply with age, taking the log of this equation gives rise to a log-log linear curve. That is plotting log incidence against log age results in a straight line.

The model is based on the observation that smoking early in life had a substantial effect on cancer in later life suggesting that smoking affected at least one early stage. Giving up smoking later in life seemed to have a substantial effect on the risk five or 10 years later suggesting that smoking affected at least one late stage.

DOLL and PETO (1978)

Using data from the British Physicians Study, Doll and Peto (1978) the following model was found to fit data for bronchial carcinoma:

$$I = c(\#\ \text{cig per day} + 6)^2(\text{age} - 22.5)^{4,\ 4.5\ \text{or}\ 5}$$

Doll and Peto used the British Physicians study and fit the model shown here to the data for smokers who started smoking at ages 16-25 and who smoked 40 or less cigarettes or less per day. $C=0.273 \times 10^{-12}$ C is constant of proportionality. The model is based on the reported number of cigarettes smoked per day and the quantity (age-22.5) represents a measure of duration of smoking when the lung cancer appeared. The 22.5 was based on the fact that the men in the study had to be between 16 and 25 years old and mean age was 19.2 years and that once it starts growing, a lung cancer probably takes only a few years to become clinically evident so that the quantity (age-22.5) is an approximation of the duration of smoking when lung cancer emerged and is a reasonable measure of time.

This suggests a quadratic dose-response relationship between the dose (number of cigarettes per day and incidence of lung cancer). Some biases discussed by Doll and Peto include: there are individual differences in mean dose per cigarette (people who get less nicotine per cigarette may smoke more cigarettes to make up for it and therefore may be misclassified; variations during life of daily cigarette consumption (light smokers at age 65 may have once been heavy or medium smokers while some who are heavy smokers at age 65 may have been light or medium smokers); and that survivors in the high group may be 'cancer proof' than average. (may cause downward curvature in the relationship of incidence with age.

LIMITATIONS OF THE A-D MODEL

- Number of cigarettes
- Duration of smoking
- Incidence curves of many human cancers other than lung cancer aren't explained by model
- Biological evidence suggests that cell proliferation and cell differentiation are important aspects of carcinogenesis.

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Number of cigarettes smoked - Is generally by self-report and is subject to recall. This number generally changes with time (Doll eliminated men who reported differences in no. of cigs smoked on different occasions).

Duration of smoking - Again is subject to recall biases and does not allow for varying periods of smoking cessation.

Doesn't explain other diseases well - While the model successively explains lung cancer incidence, it does not explain incidence of other diseases such as breast cancer and Hodgkin's Disease.

Cell proliferation and cell differentiation are not included in the AD model Based on biological evidence it is suggested that cell proliferation and cell differentiation are important aspects of carcinogenesis. These are not included in the AD model. Experiments by Hennings at al. indicate that before another genetic change occurs, initiated cells must undergo cell proliferations.